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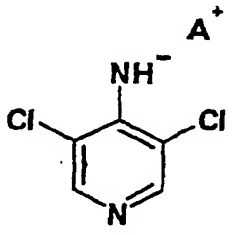
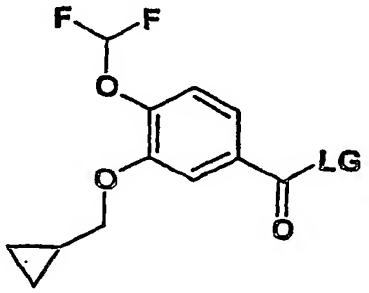
(54) Title: NOVEL PROCESS FOR THE PREPARATION OF ROFLUMILAST




(I)




(II)

(57) Abstract: The invention relates to novel processes for the preparation of high-purity roflumilast. The process involves reacting the anion of 4 - armino -3,5 dichloropyridine (I), with an activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxybenzoic acid (II), characterized in that the molar ratio of the employed anion of 4-amino-3,5 dichloropyridine to the activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxybenzoic acid is at least 1.5 and at most 3, preferably at least 1.8 and at most 2.7 particularly preferably at least 2 and at most 2.5 and very particularly preferably 2.2

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**Novel process for the preparation of roflumilast**

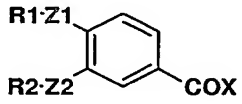
## Technical field

The present invention relates to a novel, improved process for the preparation of N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide (INN: roflumilast).

## Prior art

The international patent application WO 95/01338 describes the preparation of dialkoxy-substituted benzamides, including roflumilast, and the use thereof as PDE4 inhibitors. The international applications WO 94/02465 and WO 93/25517 also describe the preparation of dialkoxy-substituted benzamides. In the international patent application WO03/070279 oral dosage forms comprising roflumilast are described. In the international patent application WO03/099334 topically applicable pharmaceutical preparations comprising roflumilast are described. Organic Process Research & Development 2, 157-168 (1998) discloses improved processes for the preparation of 3-(cyclopentyloxy)-N-(3,5-dichloropyrid-4-yl)-4-methoxybenzamide (INN: piclamilast).

In the international applications WO 94/02465 and WO 93/25517, the dialkoxy-substituted benzamides are obtained by reacting activated benzoic acid derivatives of the general formula




with amines of the general formula $R3NH_2$. Activated benzoic acid derivatives mentioned are acid halides, especially acid chlorides or else anhydrides. The reaction may take place in the presence of a base, e.g. of an organic base such as, for example, triethylamine, in the presence of a cyclic base such as, for example, N-methylmorpholine or pyridine or else in the presence of an alkali metal hydride such as, for example, sodium hydride, in an inert solvent such as, for example, tetrahydrofuran, dimethylformamide or dichloromethane.

3-(Cyclopentyloxy)-N-(3,5-dichloropyrid-4-yl)-4-methoxybenzamide (INN: piclamilast) is obtained in WO 93/25517 by reacting 3-cyclopentyl-4-methoxybenzoic acid, which has been deprotonated with N-methylmorpholine, with 4-amino-3,5-dichloropyridine in tetrahydrofuran. In WO 94/02465, 3-(cyclopentyloxy)-N-(3,5-dichloropyrid-4-yl)-4-methoxybenzamide (INN: piclamilast) is prepared by mixing

together and subsequently melting 4-amino-3,5-dichloropyridine and 3-cyclopentyloxy-4-methoxybenzoyl chloride.

In the process for preparing roflumilast described in WO 95/01338, a solution of 0.0275 mol of 3-cyclopropylmethoxy-4-difluoromethoxybenzoyl chloride in tetrahydrofuran is added dropwise to a suspension of 0.03 mol of 4-amino-3,5-dichloropyridine and 0.066 mol of NaH (in mineral oil) in tetrahydrofuran at 15-20 °C.

In the improved process described in Organic Process Research & Development 2, 157-168 (1998) for preparing 3-(cyclopentyloxy)-N-(3,5-dichloropyrid-4-yl)-4-methoxybenzamide (INN: piclamilast), firstly 0.218 mol of KOtBu is added to 0.22 mol of 4-amino-3,5-dichloropyridine at 90 °C, and then a solution of 0.2 mol of 3-cyclopentyloxy-4-methoxybenzoyl chloride is added. The mixture is boiled under reflux for some time, cooled to 90 °C again and then a further 0.218 mol of KOtBu is added. This is followed by boiling under reflux again, before the reaction mixture is worked up by methods known to the skilled person.

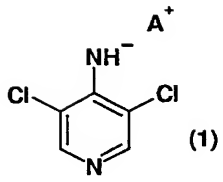
None of the processes described in the international applications WO 93/25517 and WO 94/02465 for preparing piclamilast, nor the process described in WO 95/01338 for preparing roflumilast, appear to be suitable for the industrial preparation of roflumilast of high purity.

Although the improved process described in Organic Process Research & Development 2, 157-168 (1998) for preparing 3-(cyclopentyloxy)-N-(3,5-dichloropyrid-4-yl)-4-methoxybenzamide (INN: piclamilast) has already been optimized for feasibility on the industrial scale, when applied analogously to roflumilast it leads to the formation of more than 3% by weight of the by-product N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-hydroxybenzamide, which cannot be reduced even by multiple recrystallization.

**Description of the invention**

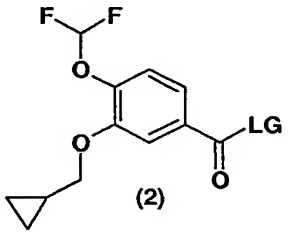
It has now been found, surprisingly, that the formation of by-products, especially of the abovementioned by-product, can be very substantially averted when an activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxybenzoic acid is reacted with an excess of the anion of 4-amino-3,5-dichloropyridine.

A first aspect of the invention is therefore a process for the preparation of roflumilast by reacting the anion of 4-amino-3,5-dichloropyridine (1)




(1)

with an activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxybenzoic acid (2),




(2)

characterized in that the molar ratio of the employed anion of 4-amino-3,5-dichloropyridine to the activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxybenzoic acid is at least 1.5 and at most 3, preferably at least 1.8 and at most 2.7, particularly preferably at least 2 and at most 2.5 and very particularly preferably 2.2.

$A^+$ in the formula 1 is a cation; $A^+$ is, for example, an alkali metal cation, preferably the potassium cation. LG in formula 2 is a suitable leaving group, preferably a chlorine atom, a bromine atom or a radical of the formula OC(O)-1-4C-alkyl. LG is particularly preferably a chlorine atom.

1-4C-alkyl in the formula OC(O)-1-4C-alkyl is a straight-chain or branched alkyl radicals having 1 to 4 carbon atoms. Examples which may be mentioned are the butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl, ethyl and methyl radicals.

Reaction of the anion of 4-amino-3,5-dichloropyridine (1) with an activated derivative of 3-cyclopropyl-methoxy-4-difluoromethoxybenzoic acid (2) can be carried out in all conventional inert solvents such as, for example, dichloromethane, toluene, xylene, dimethylformamide or N-methylpyrrolidone. The use of dimethylformamide or N-methylpyrrolidone is preferred. The use of dimethylformamide is very particularly preferred.

A further aspect of the invention is therefore one of the processes described above for preparing roflumilast, characterized in that reaction of the anion of 4-amino-3,5-dichloropyridine (1) with an activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxybenzoic acid (2) is carried out in a solvent selected from the group of dichloromethane, toluene, xylene, dimethylformamide or N-methylpyrrolidone, preferably in dimethylformamide or N-methylpyrrolidone and very preferably in dimethylformamide.

The reaction temperatures for the conversion are between 0°C and the boiling point of the solvent used. The conversion is preferably carried out at temperatures between 15 and 40°C, very particularly preferably between 20 and 30°C.

A further aspect of the invention is therefore one of the processes described above for preparing roflumilast, characterized in that reaction of the anion of 4-amino-3,5-dichloropyridine (1) with an activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxybenzoic acid (2) is carried out at a temperature between 0°C and the boiling point of the inert solvent used, preferably at a temperature between 15 and 40°C and particularly preferably at a temperature between 20 and 30°C.

In the reaction of the anion of 4-amino-3,5-dichloropyridine (1) with an activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxybenzoic acid (2) it is possible to add either the anion of 4-amino-3,5-dichloropyridine (1) or the activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxybenzoic acid (2) to the respective other reactant. However, the process in which the activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxybenzoic acid is added as second reactant to the anion of 4-amino-3,5-dichloropyridine (1) is preferred.

Activated derivatives of 3-cyclopropylmethoxy-4-difluoromethoxybenzoic acid (2) may be, for example, the corresponding acid halides, especially the acid chloride or else an anhydride [LG then corresponds to Cl, Br or OC(O)-1-4C-alkyl]. The acid halides are preferred in this connection, and the acid chloride is very particularly preferred.

A further aspect of the invention is therefore the process described above for preparing roflumilast, characterized in that the activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxybenzoic acid is a 3-cyclopropylmethoxy-4-difluoromethoxybenzoyl halide, especially 3-cyclopropylmethoxy-4-difluoromethoxybenzoyl chloride.

Strong bases selected from the group of KOtBu, NaOtBu and LiOtBu are particularly suitable for preparing the anion of 4-amino-3,5-dichloropyridine. The use of KOtBu is preferred.

A further aspect of the invention is therefore one of the processes described above for preparing roflumilast, characterized in that a base selected from the group of KOtBu, NaOtBu or LiOtBu is used to prepare the anion of 4-amino-3,5-dichloropyridine. KOtBu is preferably used.

The molar ratio of employed base to 4-amino-3,5-dichloropyridine is in this case advantageously in the range from 0.8 to 1.1 and preferably in the range from 0.9 to 1.0.

A further aspect of the invention is therefore one of the processes described above for preparing roflumilast, characterized in that the molar ratio of employed base to 4-amino-3,5-dichloropyridine in the anion formation is between 0.8 and 1.1, preferably between 0.9 and 1.0.

The activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxybenzoic acid is prepared by methods known to the skilled person.

The corresponding acid chloride is, for example, preferably prepared by reacting 3-cyclopropylmethoxy-4-difluoromethoxybenzoic acid with thionyl chloride in the presence of catalytic amounts of dimethylformamide in an inert solvent. An example of an inert solvent is toluene or xylene; the chlorination reaction is typically carried out at 70 to 90°C.

The roflumilast prepared by the processes described above is distinguished by a purity of ≥ 99% by weight. Crystallization from isopropanol/water (ratio: between 85:15 and 100:0% by volume, preferably between 90:10 and 95:5% by volume) allows the purity to be increased further to ≥ 99.8% by weight.

A further aspect of the invention is therefore one of the processes described above for preparing roflumilast, characterized in that the product resulting from the process is recrystallized in a mixture of isopropanol and water (ratio isopropanol/water: between 85:15 and 100:0% by volume, preferably between 90:10 and 95:5% by volume).

Further aspects of the invention which should be mentioned are:

Roflumilast prepared by one of the processes described above, characterized in that its purity is ≥ 99% by weight, preferably ≥ 99.8% by weight.

Roflumilast prepared by one of the processes described above, characterized in that it contains less than 0.1% by weight, preferably 0.05% by weight, of the by-product N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-hydroxybenzamide.

The processes according to the invention for the preparation of roflumilast are in particular useful for the large-scale preparation of roflumilast; high-purity roflumilast can be prepared in a scale of about 5 to 500 kg per batch.

Roflumilast prepared by one of the processes described above can be used in human and veterinary medicine for the treatment and prophylaxis, for example, of the following diseases: acute and chronic (especially inflammatory and allergen-induced) airway disorders of various etiologies (bronchitis, allergic bronchitis, bronchial asthma, emphysema, COPD); dermatoses (especially of a proliferative, inflammatory and allergic nature) such as, for example, psoriasis (vulgaris), toxic and allergic contact eczema, atopic eczema, seborrhoic eczema, lichen simplex, sunburn, pruritus in the genitoanal region, alopecia areata, hypertrophic scars, discoid lupus erythematosus, follicular and extensive pyodermas, endogenous and exogenous acne, acne rosacea and other proliferative, inflammatory and allergic skin disorders; disorders based on excessive release of TNF an leukotrienes, e.g. disorders of the arthritic type (rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis and other arthritic states), disorders of the immune system (AIDS, multiple sclerosis), types of shock [septic shock, endotoxin shock, gram-negative sepsis, toxic shock syndrome and ARDS (adult respiratory distress syndrome)] and generalized inflammations in the gastrointestinal region (Crohn's disease and ulcerative colitis); disorders based on allergic and/or chronic abnormal immunological reactions in the region of the upper airways (pharyngeal space, nose) and adjacent regions (paranasal sinuses, eyes), such as, for example, allergic rhinitis/sinusitis, chronic rhinitis/sinusitis, allergic conjunctivitis and nasal polyps; but also cardiac disorders which can be treated by PDE inhibitors, such as, for example, heart failure, or disorders which can be treated owing to the tissue-relaxant effect of PDE inhibitors, such as, for example, erectile dysfunction or colic of the kidneys and ureters connected with kidney stones; or else disorders of the CNS such as, for example, depressions or arteriosclerotic dementia.

The invention therefore further relates to roflumilast prepared by one of the processes described above for use in the treatment and/or prophylaxis of diseases, especially the diseases mentioned.

The invention also relates to the use of roflumilast prepared by one of the processes described above for the production of pharmaceutical compositions which are employed for the treatment and/or prophylaxis of the diseases mentioned. The disease is preferably an acute or chronic airway disorder (for example asthma, bronchitis, allergic rhinitis, emphysema and COPD), a dermatosis or an arthritic disorder (for example rheumatoid arthritis, rheumatoid spondylitis and osteoarthritis).

The invention furthermore relates to a method for the treatment of mammals, including humans, suffering from one of the mentioned diseases. The method is characterized in that a therapeutically effective amount of roflumilast prepared by one of the processes described above is administered together with conventional auxillaries and/or excipients to the mammal with the disease. Preferably the

disease is an acute or chronic airway disorder (for example asthma, bronchitis, allergic rhinitis, emphysema and COPD), a dermatosis or an arthritic disorder (for example rheumatoid arthritis, rheumatoid spondylitis and osteoarthritis).

The administration of the pharmaceutical compositions according to the invention may be performed in any of the generally accepted modes of administration available in the art. Illustrative examples of suitable modes of administration include intravenous, oral, nasal, parenteral, topical, transdermal and rectal delivery. Oral delivery is preferred.

The pharmaceutical compositions are prepared by processes, which are known per se and familiar to the person skilled in the art. As pharmaceutical composition, the roflumilast prepared according to one of the above-mentioned processes is either employed as such, or preferably in combination with suitable pharmaceutical auxiliaries and/or excipients, e.g. in the form of tablets, coated tablets, capsules, caplets, suppositories, emulsions, suspensions, gels or solutions, the active compound content advantageously being between 0.1 and 95% and where, by the appropriate choice of the auxiliaries and/or excipients, a pharmaceutical administration form (e.g. a delayed release form or an enteric form) exactly suited to the active compound and/or to the desired onset of action can be achieved. In the international patent application WO03/070279 oral dosage forms comprising roflumilast are described.

The person skilled in the art is familiar with auxiliaries or excipients which are suitable for the desired pharmaceutical formulations on account of his/her expert knowledge. In addition to solvents, gel formers, ointment bases and other active compound excipients, for example antioxidants, dispersants, emulsifiers, preservatives, solubilizers, colorants, complexing agents or permeation promoters, can be used.

For the treatment of disorders of the respiratory tract, the roflumilast prepared according to one of the above-mentioned processes is preferably also administered by inhalation in the form of an aerosol; the aerosol particles of solid, liquid or mixed composition preferably having a diameter of 0.5 to 10 µm, advantageously of 2 to 6 µm.

Aerosol generation can be carried out, for example, by pressure-driven jet atomizers or ultrasonic atomizers, but advantageously by propellant-driven metered aerosols or propellant-free administration of micronized active compounds from inhalation capsules.

Depending on the inhaler system used, in addition to the active compounds the administration forms additionally contain the required excipients, such as, for example, propellants (e.g. Frigen in the case

of metered aerosols), surface-active substances, emulsifiers, stabilizers, preservatives, flavorings, fillers (e.g. lactose in the case of powder inhalers) or, if appropriate, further active compounds.

For the purposes of inhalation, a large number of apparatuses are available with which aerosols of optimum particle size can be generated and administered, using an inhalation technique which is as right as possible for the patient. In addition to the use of adaptors (spacers, expanders) and pear-shaped containers (e.g. Nebulator®, Volumatic®), and automatic devices emitting a puffer spray (Autohaler®), for metered aerosols, in particular in the case of powder inhalers, a number of technical solutions are available (e.g. Diskhaler®, Rotadisk®, Turbohaler® or the inhaler described in European Patent Application EP 0 505 321), using which an optimal administration of active compound can be achieved.

For the treatment of dermatoses, the roflumilast prepared according to one of the above-mentioned processes is in particular administered in the form of those pharmaceutical compositions, which are suitable for topical application. For the production of the pharmaceutical compositions, the roflumilast prepared according to one of the above-mentioned processes is preferably mixed with suitable pharmaceutical auxiliaries and further processed to give suitable pharmaceutical formulations. Suitable pharmaceutical formulations are, for example, powders, emulsions, suspensions, sprays, oils, ointments, fatty ointments, creams, pastes, gels or solutions. In the international patent application WO03/099334 topically applicable pharmaceutical preparations comprising roflumilast are described.

The dosage of the roflumilast prepared according to one of the above-mentioned processes is in the order of magnitude customary for PDE inhibitors, it being possible to administer the daily dose in one or more dosage units. Customary dosages are disclosed for example in WO95/01338. In general, oral dosage forms contain from 0.01 mg to 5 mg, preferably from 0.05 mg to 2.5 mg, particularly preferably 0.1 mg to 0.5 mg of roflumilast per dosage unit. Dosage forms for topical administration contain from 0.005 mg to 5 mg, preferably 0.01 mg to 2.5 mg particularly preferably 0.1 mg to 0.5 mg of roflumilast per dosage unit. Typically, pharmaceutical compositions of the invention contain 0.01 mg, 0.1 mg, 0.125 mg, 0.25 mg or 0.5 mg of roflumilast per dosage unit.

The following examples serve to illustrate the invention further without restricting it.

**Synthesis of roflumilast - coupling step**

The potassium salt suspension of the anion of 4-amino-3,5-dichloropyridine in DMF (2-2.5 equivalents) is introduced into a reaction vessel. A solution of 3-cyclopropylmethoxy-4-difluoromethoxybenzoyl chloride (1 equivalent) in DMF is slowly added to this suspension while stirring vigorously at a temperature of 15 to 40°C, preferably 20 to 30°C. After the reaction is complete, water is slowly added while stirring at 15-25°C, and the pH is adjusted to 2-3 with hydrochloric acid.

The solid is centrifuged or filtered, washed with water, resuspended in a sodium hydroxide solution (pH = 9-10), centrifuged or filtered again and washed with water. This moist crude material is, if desired, subjected to a recrystallization from an isopropanol/water mixture (ratio between 85:15 and 100:0, preferably 95:5% by volume). The resulting product is centrifuged or filtered and dried in vacuo at a temperature not exceeding 60°C.

**Synthesis of 3-cyclopropylmethoxy-4-difluoromethoxybenzoyl chloride**

A reaction vessel is charged with toluene, a catalytic amount of DMF (1–5% by weight of the amount of thionyl chloride employed) and 1 equivalent of 3-cyclopropylmethoxy-4-difluoromethoxybenzoic acid. While stirring, 1 to 4 equivalents of thionyl chloride are slowly added at 70 to 90°C.

After the reaction is complete, the reaction mixture is concentrated in vacuo at 45 to 60°C, and the solvent toluene is replaced by DMF; the resulting 3-cyclopropylmethoxy-4-difluoromethoxybenzoyl chloride solution is used without further purification in the subsequent coupling step.

**Synthesis of the potassium salt of 4-amino-3,5-dichloropyridine**

A reaction vessel is charged with DMF and 4-amino-3,5-dichloropyridine (1 equivalent). While stirring vigorously, potassium tert-butoxide (0.8-1.1, preferably 0.9-1.0 equivalent) is added in portions at a temperature between 15 and 30°C. A suspension of the potassium salt of the anion of 4-amino-3,5-dichloropyridine is obtained and is employed without further purification for the subsequent coupling step.

**Process A:** Standard process as described above; synthesis of the potassium salt of 4-amino-3,5-dichloropyridine using 1 equivalent of 4-amino-3,5-dichloropyridine and 1 equivalent of potassium tert-butoxide.

**Process B**: Differing from process A in that the potassium salt of 4-amino-3,5-dichloropyridine is prepared using 1 equivalent of 4-amino-3,5-dichloropyridine and 0.91 equivalent of potassium tert-butoxide.

**Process C**: Differing from the standard process in that N-methylpyrrolidone is used as solvent instead of DMF in the coupling step and in the preparation of the potassium salt of 4-amino-3,5-dichloropyridine.

**Process D**: Differing from the standard process in that only 1.8 equivalents, instead of 2-2.5 equivalents, of the potassium salt of 4-amino-3,5-dichloropyridine are employed in the coupling step.

**Process E**: Differing from the standard process in that 2.7 equivalents, instead of 2-2.5 equivalents, of the potassium salt of 4-amino-3,5-dichloropyridine are employed in the coupling step.

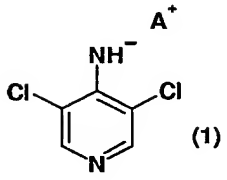
**Process F**: Differing from the standard process in that the potassium salt of 4-amino-3,5-dichloropyridine is prepared using 1 equivalent of 4-amino-3,5-dichloropyridine and 1.83 equivalents of potassium tert-butoxide.

**Process G**: The improved process described in Organic Process Research & Development 2, 157-168 (1998) for preparing piclamilast (coupling step) is applied analogously to the preparation of roflumilast.

| Process | Purity after recrystallization from isopropanol/water (data in % by weight) | Content of by-product N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-hydroxy-benzamide (data in % by weight) |
|---|---|---|
| A | ≥ 99.8 | < 0.05 |
| B | ≥ 99.8 | < 0.05 |
| C | ≥ 99.8 | < 0.05 |
| D | ≥ 99.8 | < 0.05 |
| E | ≥ 99.8 | < 0.05 |
| F | 96.2 | 0.8 |
| G | 95.4 | 3.47 |

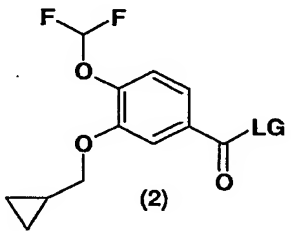
Claims

1. Process for the preparation of roflumilast by reacting the anion of 4-amino-3,5-dichloro-pyridine (1)




(1)

in which $A^+$ is a cation, preferably an alkali metal cation and particularly preferably a potassium cation, with an activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxybenzoic acid (2),




(2)

in which LG is a suitable leaving group, preferably a chlorine atom, a bromine atom or a radical of the formula OC(O)-1-4C-alkyl, and particularly preferably a chlorine atom,
characterized in that the molar ratio of the employed anion of 4-amino-3,5-dichloropyridine (1) to the activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxybenzoic acid (2) is at least 1.5 and at most 3.

2. Process according to Claim 1, characterized in that the molar ratio of the employed anion of 4-amino-3,5-dichloropyridine (1) to the activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxy-benzoic acid (2) is at least 1.8 and at most 2.7.

3. Process according to Claim 1, characterized in that the molar ratio of the employed anion of 4-amino-3,5-dichloropyridine (1) to the activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxy-benzoic acid (2) is at least 2 and at most 2.5.

4. Process according to Claim 1, characterized in that the molar ratio of the employed anion of 4-amino-3,5-dichloropyridine (1) to the activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxy-benzoic acid (2) is 2.2.

5. Process according to any of Claims 1 to 4, characterized in that the reaction of the anion of 4-amino-3,5-dichloropyridine (1) with an activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxybenzoic acid (2) is carried out in a solvent selected from the group of dichloromethane, toluene, xylene, dimethylformamide or N-methylpyrrolidone.

6. Process according to any of Claims 1 to 4, characterized in that the reaction of the anion of 4-amino-3,5-dichloropyridine (1) with an activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxybenzoic acid (2) is carried out in a dimethylformamide.

7. Process according to any of Claims 1 to 6, characterized in that the reaction of the anion of 4-amino-3,5-dichloropyridine (1) with an activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxybenzoic acid (2) is carried out a temperature between 0°C and the boiling point of the inert solvent used.

8. Process according to any of Claims 1 to 6, characterized in that the reaction of the anion of 4-amino-3,5-dichloropyridine (1) with an activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxybenzoic acid (2) is carried out a temperature between 20°C and 30°C

9. Process according to any of Claims 1 to 8, characterized in that the activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxybenzoic acid (2) is 3-cyclopropylmethoxy-4-difluoromethoxy-benzoyl chloride.

10. Process according to any of Claims 1 to 8, characterized in that the activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxybenzoic acid (2) is 3-cyclopropylmethoxy-4-difluoromethoxy-benzoyl bromide.

11. Process according to any of Claims 1 to 8, characterized in that the activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxybenzoic acid (2) is a 3-cyclopropylmethoxy-4-difluoromethoxy-benzoic acid 1-4C-alkyl-ester.

12. Process according to any of Claims 1 to 11, characterized in that a strong base selected from the group of KOtBu, NaOtBu and LiOtBu is used to prepare the anion of 4-amino-3,5-dichloropyridine.

13. Process according to Claim 12, characterized in that KOtBu is used to prepare the anion of 4-amino-3,5-dichloropyridine (1).

14. Process according to any of Claims 1 to 13, characterized in that the product resulting from the process is recrystallized in a mixture of isopropanol and water (ratio isopropanol/water: between 85:15 and 100:0% by volume, preferably between 90:10 and 95:5% by volume).

15. Roflumilast prepared by a process according to any of Claims 1 to 14.

16. Roflumilast prepared by a process according to any of Claims 1 to 14, characterized in that the purity is ≥ 99% by weight, preferably ≥ 99.8% by weight.

17. Roflumilast prepared by a process according to any of Claims 1 to 14, characterized in that it contains less than 0.1% by weight, preferably less than 0.05% by weight, of the by-product N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-hydroxybenzamide.

18. Roflumilast prepared according to Claim 15, 16 or 17 for use in the treatment of diseases.

19. Pharmaceutical compositions containing roflumilast prepared according to Claim 15, 16 or 17 together with conventional pharmaceutical auxiliaries and/or excipients.

20. Use of the roflumilast prepared according to Claim 15, 16 or 17 for the production of pharmaceutical compositions for the treatment of an acute or chronic airway disorder, a dermatosis or an arthritic disorder.

21. Method for the treatment of mammals, including humans, suffering from an acute or chronic airway disorder, a dermatosis or an arthritic disorder, characterized in that a therapeutically effective amount of the roflumilast prepared according to Claim 15, 16 or 17 is administered together with conventional auxiliaries and/or excipients to the mammal with the disorder.

INTERNATIONAL SEARCH REPORT

ational Application No
/EP2004/050272

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D213/75

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | WO 95/01338 A (BYK GULDEN LOMBERG CHEM FAB ; AMSCHLER HERMANN (DE)) 12 January 1995 (1995-01-12) cited in the application | 1-14 |
| X | page 14; example 1 | 15-21 |
| Y | WO 93/25517 A (CELLTECH LTD) 23 December 1993 (1993-12-23) cited in the application page 22; example 18 | 1-14 |

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 30 June 2004 | 12/07/2004 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Kollmannsberger, M |

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | COOK, D. C. ET AL.: "Process development of the PDE IV inhibitor 3-(cyclopentyloxy)-N-(3,5-dichlorpyrid-4-yl)-4-methoxybenzamide" ORGANIC PROCESS RESEARCH AND DEVELOPMENT, vol. 2, no. 3, 1998, pages 157-168, XP002247911 cited in the application page 161, column 2 page 164, column 2 ----- | 1-14 |

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/EP2004/050272

**Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 21is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|---|---|---|---|---|
| WO 9501338 A | 12-01-1995 | AT | 217612 T | 15-06-2002 |
| | | AU | 687087 B2 | 19-02-1998 |
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| | | PL | 311820 A1 | 18-03-1996 |
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| | | DE | 69309030 T2 | 25-09-1997 |
| | | DK | 607373 T3 | 13-10-1997 |
| | | EP | 0607373 A1 | 27-07-1994 |
| | | ES | 2102036 T3 | 16-07-1997 |
| | | WO | 9325517 A1 | 23-12-1993 |
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D213/

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | WO 95/01338 A (BYK GULDEN LOMBERG CHEM FAB ; AMSCHLER HERMANN (DE)) 12 January 1995 (1995-01-12) cited in the application | 1-14 |
| X | page 14; example 1 | 15-21 |
| Y | WO 93/25517 A (CELLTECH LTD) 23 December 1993 (1993-12-23) cited in the application page 22; example 18 | 1-14 |

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 30 June 2004 | 12/07/2004 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Kollmannsberger, M |

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | COOK, D. C. ET AL.: "Process development of the PDE IV inhibitor 3-(cyclopentyloxy)-N-(3,5-dichlorpyrid-4-yl)-4-methoxybenzamide" ORGANIC PROCESS RESEARCH AND DEVELOPMENT, vol. 2, no. 3, 1998, pages 157-168, XP002247911 cited in the application page 161, column 2 page 164, column 2 ----- | 1-14 |

# INTE[redacted]TIONAL SEARCH REPORT

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 21is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

# PATENT COOPERATION TREATY

# PCT

# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference<br>1117WOORD01 | **FOR FURTHER ACTION** | See Form PCT/IPEA/416 |
|---|---|---|
| International application No.<br>PCT/EP2004/050272 | International filing date *(day/month/year)*<br>08.03.2004 | Priority date *(day/month/year)*<br>10.03.2003 |

International Patent Classification (IPC) or national classification and IPC
C07D213/75

Applicant
ALTANA PHARMA AG

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

| | | |
|---|---|---|
| ☒ | Box No. I | Basis of the opinion |
| ☐ | Box No. II | Priority |
| ☒ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☐ | Box No. VI | Certain documents cited |
| ☐ | Box No. VII | Certain defects in the International application |
| ☐ | Box No. VIII | Certain observations on the international application |

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 15.09.2004 | 01.02.2005 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d | Authorized Officer<br>Kollmannsberger, M |

**Box No. I Basis of the report**

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   **Description, Pages**

   1-10 as originally filed

   **Claims, Numbers**

   1-21 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 21

because:

☒ the said international application, or the said claims Nos. 21 relate to the following subject matter which does not require an international preliminary examination (specify):

**see separate sheet**

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

| | | |
|---|---|---|
| the written form | ☐ | has not been furnished |
| | ☐ | does not comply with the standard |
| the computer readable form | ☐ | has not been furnished |
| | ☐ | does not comply with the standard |

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1-14 |
| | No: | Claims | 15-21 |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 1-21 |
| Industrial applicability (IA) | Yes: | Claims | 1-20 |
| | No: | Claims | |

2. Citations and explanations (Rule 70.7):

**see separate sheet**

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claim 21 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

V-1. State of the art

Reference is made to the following documents:

D1: WO 95/01338 A (BYK GULDEN LOMBERG CHEM FAB ; AMSCHLER HERMANN (DE)) 12 January 1995 (1995-01-12)

D2: WO 93/25517 A (CELLTECH LTD) 23 December 1993 (1993-12-23)

D3: COOK, D. C. ET AL.: "Process development of the PDE IV inhibitor 3-(cyclopentyloxy)-N-(3,5-dichlorpyrid-4-y l)-4-methoxybenzamide" ORGANIC PROCESS RESEARCH AND DEVELOPMENT, vol. 2, no. 3, 1998, pages 157-168, XP002247911

V-1. Novelty (Art. 33(2) PCT):

Claims 15 to 21 lack novelty. Roflumilast and its uses are known (see e. g. D1, in particular page 14 example 1). Even if the product prepared by the claimed process should differ in purity from the product disclosed in D1 these claims are not considered novel. It is the opinion of the ISA that, since purification techniques such as chromatography, distillation or recrystallisation are commonly known, the disclosure of a low molecular chemical compound is considered to make it available in **all levels of purity** unless there is evidence that until now all attempts

of purification by conventional techniques have failed. This does not appear to be the case here.

Process claims 1-14 are novel over D1 (example 1) because of the claimed ratio of the reagents and over D2 and D3 because these documents deal with piclamilast instead of roflumilast.

V-2. Inventive step (Art. 33(3) PCT)

Closest prior art for the process claims is seen in D1 (example 1 on page 14) since it deals with the synthesis of the same compound. The difference with respect to D1 is to use of the amino anion (1) in excess (cf. claim 1) with respect to the acid derivative (2) whereas in D1 substantially equimolar amounts are used. From D2 it is known that in analogous processes (preparation of piclamilast) the amine anion can be used in excess (cf. D2 examples 15 and 18). The claimed process must thus be seen as an obvious alternative of the process disclosed in D1.

The problem which is to be solved by the present application is the provision of an improved process for the preparation of roflumilast which does not lead to the formation of particular by-products (see page 2 of the description). The application contains comparative data (see table on page 10) which show that the claimed process shows some improvements with respect to a process known from D3 which was optimized for the synthesis of piclamilast. However, the process of D3 differs from the process disclosed in D1 not only in the different ratio of the starting materials but also in other parameters (e. g. the solvent). To show an unexpected improvement with respect to the closest prior art (i. e. example 1 of D1) comparative data would have to be submitted which differ only in the distinguishing feature, i. e. the molar ratio of the starting materials. In the absence of such data Art. 33(2) PCT is not fulfilled for claims 1-14.

Claims 15-21 are not novel and thus also not inventive.

| Patent document cited in search report | | Publication date | Patent family member(s) | | Publication date |
|---|---|---|---|---|---|
| WO 9501338 | A | 12-01-1995 | AT | 217612 T | 15-06-2002 |
| | | | AU | 687087 B2 | 19-02-1998 |
| | | | AU | 7490794 A | 24-01-1995 |
| | | | CA | 2165192 A1 | 12-01-1995 |
| | | | CN | 1126468 A ,B | 10-07-1996 |
| | | | CZ | 9600001 A3 | 12-06-1996 |
| | | | DE | 59410119 D1 | 20-06-2002 |
| | | | DK | 706513 T3 | 09-09-2002 |
| | | | WO | 9501338 A1 | 12-01-1995 |
| | | | EP | 0706513 A1 | 17-04-1996 |
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| **0** | **For receiving Office use only** | |
| **0-1** | International Application No. | |
| **0-2** | International Filing Date | |
| **0-3** | Name of receiving Office and "PCT International Application" | |

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| **0-4** | **Form - PCT/RO/101 PCT Request** | |
| 0-4-1 | Prepared Using | PCT Online Filing<br>Version 3.50 (Build 0001.159) |
| **0-5** | **Petition**<br>The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty | |
| **0-6** | **Receiving Office (specified by the applicant)** | European Patent Office (EPO) (RO/EP) |
| **0-7** | **Applicant's or agent's file reference** | 1117WOORD01 |
| **I** | **Title of Invention** | NOVEL PROCESS FOR THE PREPARATION OF ROFLUMILAST |
| **II** | **Applicant** | |
| II-1 | This person is: | applicant only |
| II-2 | Applicant for | all designated States except US |
| II-4 | Name: | ALTANA PHARMA AG |
| II-5 | Address: | Byk-Gulden-Str. 2<br>78467 Konstanz<br>Germany |
| II-6 | State of nationality | DE |
| II-7 | State of residence | DE |
| II-8 | Telephone No. | +49-(0)7531-84-5295 |
| II-9 | Facsimile No. | +49-(0)7531-84-5321 |
| II-10 | e-mail | DEKON.IPPA-DE@altanapharma.com |
| **III-1** | **Applicant and/or inventor** | |
| III-1-1 | This person is: | applicant and inventor |
| III-1-2 | Applicant for | US only |
| III-1-4 | Name (LAST, First) | KOHL, Bernhard |
| III-1-5 | Address: | Zum Bruehl 9<br>78465 Konstanz<br>Germany |
| III-1-6 | State of nationality | DE |
| III-1-7 | State of residence | DE |

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| **III-2** | **Applicant and/or inventor** | |
| III-2-1 | This person is: | applicant and inventor |
| III-2-2 | Applicant for | US only |
| III-2-4 | Name (LAST, First) | MUELLER, Bernd |
| III-2-5 | Address: | Buecklestr. 84a<br>78467 Konstanz<br>Germany |
| III-2-6 | State of nationality | DE |
| III-2-7 | State of residence | DE |
| **III-3** | **Applicant and/or inventor** | |
| III-3-1 | This person is: | applicant and inventor |
| III-3-2 | Applicant for | US only |
| III-3-4 | Name (LAST, First) | PALOSCH, Walter |
| III-3-5 | Address: | Junkernbuehl 39<br>78239 Rielasingen<br>Germany |
| III-3-6 | State of nationality | DE |
| III-3-7 | State of residence | DE |
| **IV-1** | **Agent or common representative; or address for correspondence** | |
| | The person identified below is hereby/ has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: | agent |
| IV-1-1 | Name (LAST, First) | RUPP, Herbert |
| IV-1-2 | Address: | c/o ALTANA Pharma AG, Byk-Gulden-Str. 2<br>78467 Konstanz<br>Germany |
| IV-1-3 | Telephone No. | +49(0)7531-84-5314 |
| IV-1-4 | Facsimile No. | +49(0)7531-84-5321 |
| IV-1-5 | e-mail | DEKON.IPPA-DE@altanapharma.com |
| IV-1-6 | Agent's registration No. | 00052372.0 |
| **V** | **DESIGNATIONS** | |
| **V-1** | **The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.** | |

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| **VI-1** | **Priority claim of earlier regional application** | | |
| VI-1-1 | Filing date | 10 March 2003 (10.03.2003) | |
| VI-1-2 | Number | 03005245.0 | |
| VI-1-3 | Regional Office | EP | |
| **VI-2** | **Priority document request** | | |
| | The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s): | VI-1 | |
| **VII-1** | **International Searching Authority Chosen** | European Patent Office (EPO) (ISA/EP) | |
| **VII-2** | **Request to use results of earlier search; reference to that search** | | |
| **VII-2-1** | Date | 16 July 2003 (16.07.2003) | |
| VII-2-2 | Number | 03005245 | |
| VII-2-3 | Country (or regional Office) | EP | |
| **VIII** | **Declarations** | Number of declarations | |
| VIII-1 | Declaration as to the identity of the inventor | - | |
| VIII-2 | Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent | 1 | |
| VIII-3 | Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application | - | |
| VIII-4 | Declaration of inventorship (only for the purposes of the designation of the United States of America) | 1 | |
| VIII-5 | Declaration as to non-prejudicial disclosures or exceptions to lack of novelty | - | |

| | | |
|---|---|---|
| VIII-4-1 | **Declaration: Inventorship (only for the purposes of the designation of the United States of America)**<br>Declaration of Inventorship (Rules 4.17(iv) and 51bis.1(a)(iv)) for the purposes of the designation of the United States of America: | I hereby declare that I believe I am the original, first and sole (if only one inventor is listed below) or joint (if more than one inventor is listed below) inventor of the subject matter which is claimed and for which a patent is sought.<br>This declaration is directed to the international application of which it forms a part (if filing declaration with application).<br>I hereby declare that my residence, mailing address, and citizenship are as stated next to my name.<br>I hereby state that I have reviewed and understand the contents of the above-identified international application, including the claims of said application. I have identified in the request of said application, in compliance with PCT Rule 4.10, any claim to foreign priority, and I have identified below, under the heading "Prior Applications", by application number, country or Member of the World Trade Organization, day, month, and year of filing, any application for a patent or inventor's certificate filed in a country other than the United States of America, including any PCT international application designating at least one country other than the United States of America, having a filing date before that of the application on which foreign priority is claimed. |
| VIII-4-1-1 | Prior applications: | |

| | | |
|---|---|---|
| | | I hereby acknowledge the duty to disclose information that is known by me to be material to patentability as defined by 37 C.F.R. § 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the PCT international filing date of the continuation-in-part application.<br>I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon. |
| VIII-4-1-1-1 | Name (LAST, First) | KOHL, Bernhard |
| VIII-4-1-1-2 | Residence:<br>(city and either US State, if applicable, or country) | Konstanz, Germany |
| VIII-4-1-1-3 | Mailing address: | Zum Bruehl 9 D-78465 Konstanz Germany |
| VIII-4-1-1-4 | Citizenship: | DE |
| VIII-4-1-1-5 | Inventor's Signature:<br>(if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent) | /Bernhard KOHL/ Bernhard Kohl<br>22 March 2004 |
| VIII-4-1-1-6 | Date:<br>(of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application) | ~~08 March 2004 (08.03.2004)~~ |

| | | |
|---|---|---|
| VIII-4-1-2-1 | Name (LAST, First) | MUELLER, Bernd |
| VIII-4-1-2-2 | Residence: (city and either US State, if applicable, or country) | Konstanz, Germany |
| VIII-4-1-2-3 | Mailing address: | Buecklestr. 84a D-78467 Konstanz Germany |
| VIII-4-1-2-4 | Citizenship: | DE |
| VIII-4-1-2-5 | Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent) | /Bernd MUELLER/ 22 March 2004 |
| VIII-4-1-2-6 | Date (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application) | ~~08 March 2004 (08.03.2004)~~ |
| VIII-4-1-3-1 | Name (LAST, First) | PALOSCH, Walter |
| VIII-4-1-3-2 | Residence: (city and either US State, if applicable, or country) | Rielasingen, Germany |
| VIII-4-1-3-3 | Mailing address: | Junkernbuehl 39 D-78239 Rielasingen Germany |
| VIII-4-1-3-4 | Citizenship: | DE |
| VIII-4-1-3-5 | Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent) | /Walter PALOSCH/ 22 March 2004 |
| VIII-4-1-3-6 | Date (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application) | ~~08 March 2004 (08.03.2004)~~ |

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| IX | Check list | number of sheets | electronic file(s) attached |
|---|---|---|---|
| IX-1 | Request (including declaration sheets) | 8 | ✓ |
| IX-2 | Description | 10 | ✓ |
| IX-3 | Claims | 3 | ✓ |
| IX-4 | Abstract | 1 | ✓ |
| IX-5 | Drawings | 0 | ✓ |
| IX-7 | TOTAL | 22 | |
| | **Accompanying Items** | paper document(s) attached | electronic file(s) attached |
| IX-8 | Fee calculation sheet | - | ✓ |
| IX-17 | PCT-SAFE physical media | - | - |
| **IX-19** | **Figure of the drawings which should accompany the abstract** | | |
| **IX-20** | **Language of filing of the international application** | English | |
| **X-1** | **Signature of applicant, agent or common representative** | | |
| **X-1-1** | Name (LAST, First) | | |
| **X-1-2** | Name of signatory | | |
| **X-1-3** | Capacity | | |

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| **10-1** | **Date of actual receipt of the purported international application** | |
| **10-2** | **Drawings:** | |
| 10-2-1 | Received | |
| 10-2-2 | Not received | |
| **10-3** | **Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application** | |
| **10-4** | **Date of timely receipt of the required corrections under PCT Article 11(2)** | |
| **10-5** | **International Searching Authority** | ISA/EP |
| **10-6** | **Transmittal of search copy delayed until search fee is paid** | |

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| **11-1** | **Date of receipt of the record copy by the International Bureau** | |